VERIFIED TRANSLATION OF PCT

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Modified

Annex AU.IV

VERIFICATION OF TRANSLATION

I, Dr Anthony J Wickens,

of 24 Honeypots Road, Mayford, Woking, Surrey, England

declare as follows:

1. That I am well acquainted with both the English and German languages, and

2. That the attached document is a true and correct translation made by me to the best of my knowledge and belief of:-

(b) The Amendments made to the specification
International Application No. PCT/EP96/03229

12th January 1998

(Date)

(Signature of Translator)

A hormone patch

The present invention relates to a patch to be applied to the skin, which is also termed a transdermal therapeutic system (TTS).

Dermal patches for the transdermal administration of drug substances are known. One problem with these preparations is the resorption of sufficiently large amounts of active ingredient per unit area and per unit time, because many drug substances which are deposited on or stuck on to the skin in a topical preparation do not pass through the skin in sufficient amounts.

For this reason, so-called resorption accelerators, which are also termed penetration improvers, resorption promoters or enhancers, have been investigated and have been incorporated in dermal patches. In this manner, it has often been possible to achieve the desired pharmacological effect for the first time. Examples of resorption accelerators include propylene glycol, polyethylene glycols of lower molecular weight, oleic acid, isopropyl myristate, myristol, "Gattefossé" Transcutol, "Henkel" Eutanol, glycerol monolaurate (="Hüls" Imvitor 312), a partial glyceride of ricinoleic acid (="Hüls" Softigen 701), unsaturated polyglycolised glycerides (="Gattefossé" Labrafil M1944CS), "Gattefossé" Labrafac Hydro WL1219, Estasan GT60, saturated polyglycolised glycerides (="Gattefossé" Labrasol), phospholipids, etc. Further literature thereon: Rieg-Falson, F. *et al.* 1989, Watkinson, A.C. *et al.* 1991, and Hadgraft, J. and Guy, R.H. (eds.): Marcel Dekker Inc. N.Y. 1989.

A transdermal therapeutic system (TTS) having a backing film and having an acrylate-based pressure-sensitive adhesive, having a hormone content and a content of a plurality of resorption accelerators, is already known from WO-A-96/08 255, wherein

the hormone content is provided by a content of levonorgestrel, and wherein

- the resorption accelerators may comprise, amongst others, a C_{8-22} fatty acid such as oleic acid (page 6, line 25), or 2-(2-ethoxyethoxy)-ethanol; a *mixture of oleic acid and* 2-(2-ethoxyethoxy)-ethanol *per se* is not cited; claim 1.

Acrylate-based pressure-sensitive adhesives form part of the prior art, such as those based on DUROTAK® for example, which are obtainable by the radical polymerisation of butyl acrylate, 2-ethylhexyl acrylate, methacrylate, vinyl acetate, acrylic acid and/or hydroxyethyl acrylate; see the list of monomers for DUROTAK® 280-2287, for example.

Compared with this prior art, the present invention relates to a transdermal therapeutic system (TTS) transdermal therapeutic system (TTS) having a backing film, having an acrylate-based pressure-sensitive adhesive, having a hormone content and a content of resorption accelerators and having a protective film, wherein

- the hormone content is provided by a content of oestrogen and/or gestagen and/or androgen, and wherein

- the resorption accelerators are the two substances oleic acid and 2-(2-ethoxyethoxy)-ethanol.

The present invention therefore relates to a patch to be applied to the skin, which is also termed a transdermal therapeutic system (TTS), in which up to three drug substances are contained which are released from the TTS, through the skin, into the body (systemic circulation) of the human or of the animal. The dermal patch consists of a backing film and a pressure-sensitive adhesive in which the drug substances as well as other substances, for example resorption accelerators, are situated. In addition, a further adhesive layer is optionally provided, as is a protective film, which is removed by pulling it off before the patch is used.

Therefore, this invention also relates to the use of a mixture of the two substances oleic acid and 2-(2-ethoxyethoxy)ethanol jointly in a TTS as enhancers for oestrogens such as oestradiol and ethinyl oestradiol, gestagens such as norethisterone acetate, levonorgestrel or chlormadinone acetate and/or androgens such as testosterone.

Moreover, it should also be emphasised as being advantageous that these are two known substances, which are customary and harmless as adjuvant substances in pharmaceutical preparations, and are not new chemical substances which would involve the risk of side-effects and would have to be tested in long-term toxicological investigations before they could be employed in a medicine for human use.

This invention further relates to a transdermal therapeutic system which is characterised in that the oestrogen can be oestradiol or ethinyl oestradiol and the gestagen can be norethisterone acetate, levonorgestrel, progesterone or chlormadinone acetate, and the androgen can be testosterone, wherein these hormones can also be used in the form of other salts or esters, or of the bases also.

The transdermal therapeutic system according to the invention may be characterised in that the acrylate-based pressure-sensitive adhesive is obtained by the radical polymerisation of butyl acrylate, 2-ethylhexyl acrylate, methacrylate, vinyl acetate, acrylic acid, hydroxyethyl acrylate or from mixtures of some or all of the cited monomers, and/or that crosslinking agents and/or other adjuvant substances have been added in an amount less than 2 %.

The transdermal therapeutic system according to the invention may further be characterised in that the ratio by weight of oleic acid to 2-(2-ethoxyethoxy)-ethanol is 2:1 to 1:2, preferably 1.5:1 to 1:1.5, and the amount of this mixture is 1 - 10 percent by weight with respect to the TTS weight, including all the active ingredients and adjuvant substances, but without the films such as the backing film and the release liner.

The transdermal therapeutic system according to the invention may further be characterised in that it contains

- oestradiol and norethisterone acetate, or
- oestradiol and levonorgestrel, or
- ethinyl oestradiol and levonorgestrel, or
- testosterone.

Example and comparative examples 1 to 5

In the context of our work on the development of dermal patches comprising different drug substances, a very large number of penetration improvers has been incorporated in the formulation, and the release of the active ingredient has been investigated. The latter has been tested in the USP paddle apparatus (described in United States Pharmacopoeia XXIII), penetration through "hairless mouse skin" has been tested using the Franz cell model (Franz cell: Franz, T.J., J. Invest. Dermatol. 1975 (64), pages 191-195), and penetration through human stratum corneum has likewise been tested in the Franz cell. The penetration-promoting substances comprised oleic acid DAB 10, 2-(2-ethoxyethoxy)ethanol, Eutanol G (DAB 10), Labrafac and Labrafil, as well as mixtures comprising oleic acid/2-(2-ethoxyethoxy)ethanol, oleic acid/Labrafil, and oleic acid/Labrafac, in a ratio of approximately 1:1.

The release of active ingredient with time in the USP paddle apparatus exhibited no great differences.

On measuring the permeation through animal skin, and particularly through human stratum corneum, however, it was shown that dermal patches which were produced with a mixture of oleic acid and 2-(2-ethoxyethoxy)ethanol in a ratio of approximately 1:1 as enhancers gave significantly higher permeation rates than those which were observed on the addition of the individual enhancers or without enhancers. It was surprising that the mixture of oleic acid and 2-(2-ethoxyethoxy)ethanol gave permeation rates which were higher than those obtained when

using mixtures of oleic acid and other enhancers. The former mixture is obviously distinguished by its special resorption-accelerating properties.

An HPLC method such as that which is familiar to one skilled in the art was employed for the analysis of the active ingredient content in the acceptor medium.

CLAIMS

1. A transdermal therapeutic system (TTS) having a backing film, having an acrylate-based pressure-sensitive adhesive, having a hormone content and a content of resorption accelerators and having a protective film, wherein

- the hormone content is provided by a content of oestrogen and/or gestagen and/or androgen, and wherein

- the resorption accelerators are the two substances oleic acid and 2-(2-ethoxyethoxy)-ethanol.

2. A transdermal therapeutic system (TTS) according to claim 1, *characterised* in that the oestrogen is oestradiol or ethinyl oestradiol and the gestagen is norethisterone acetate, levonorgestrel, progesterone or chlormadinone acetate, and the androgen is testosterone, wherein these hormones can also be used in the form of other salts or esters, or of the bases also.

3. A transdermal therapeutic system (TTS) according to claim 1 or 2, *characterised* in that the acrylate-based pressure-sensitive adhesive has been obtained by the radical polymerisation of butyl acrylate, 2-ethylhexyl acrylate, methacrylate, vinyl acetate, acrylic acid, hydroxyethyl acrylate or from mixtures of some or all of the cited monomers, and/or that crosslinking agents and/or other adjuvant substances have been added in an amount less than 2 %.

4. A transdermal therapeutic system (TTS) according to any one of claims 1 to 3, *characterised* in that the ratio by weight of oleic acid to 2-(2-ethoxyethoxy)ethanol is 2:1 to 1:2, preferably 1.5:1 to 1:1.5, and the amount of this mixture is 1 - 10 percent by

percent by weight with respect to the TTS weight, including all the active ingredients and adjuvant substances, but without the films such as the backing film and the release liner.

5. A transdermal therapeutic system (TTS) according to any one of claims 1 to 4, *characterised* in that oleic acid and 2-(2-ethoxyethoxy)ethanol have been incorporated in a ratio of approximately 1:1.

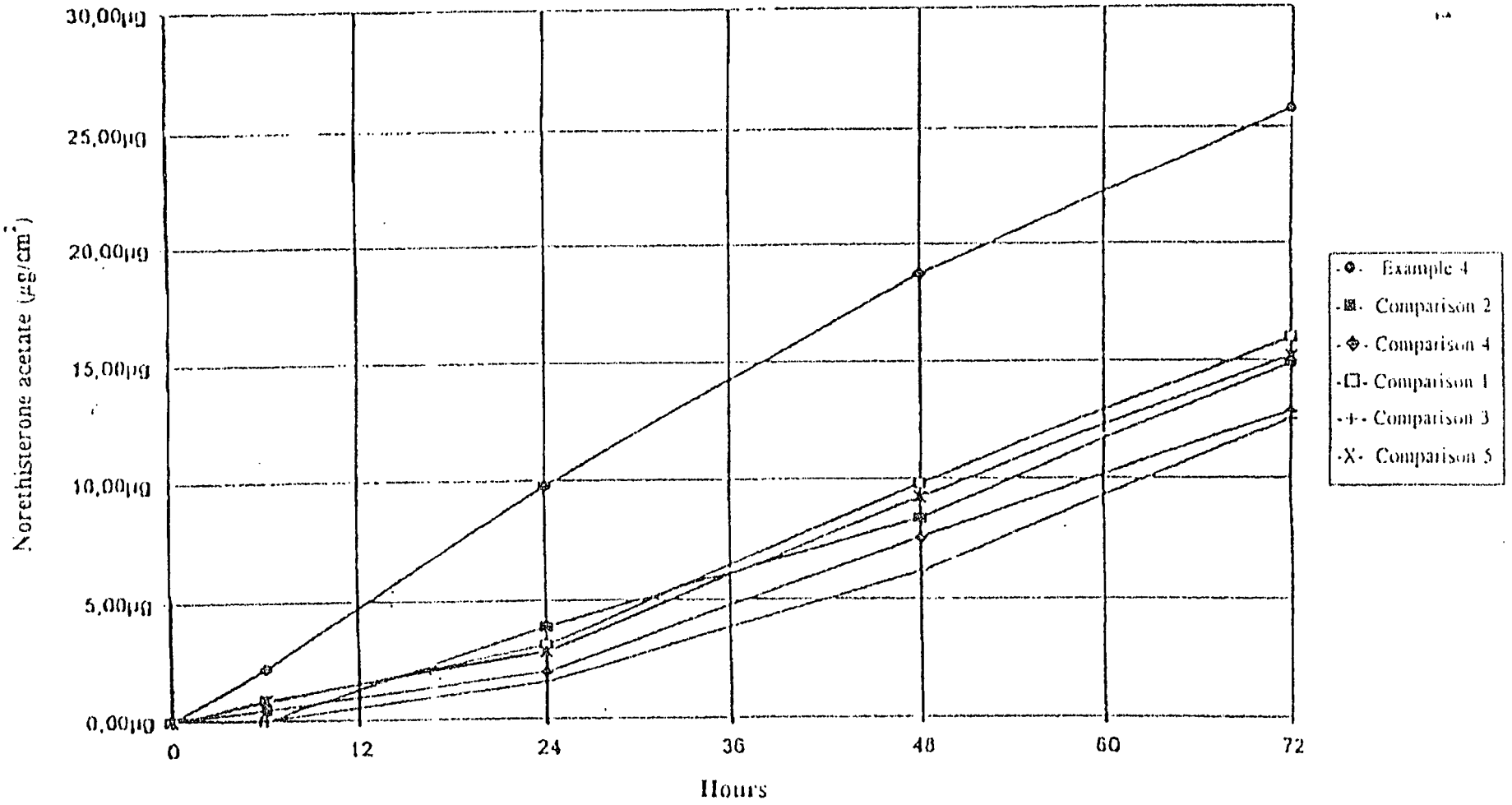
6. A transdermal therapeutic system (TTS) according to any one of claims 1 to 5, *characterised* in that it contains oestradiol and norethisterone acetate.

7. A transdermal therapeutic system (TTS) according to any one of claims 1 to 5, *characterised* in that it contains oestradiol and levonorgestrel.

8. A transdermal therapeutic system (TTS) according to any one of claims 1 to 5, *characterised* in that it contains ethinyl oestradiol and levonorgestrel.

9. A transdermal therapeutic system (TTS) according to any one of claims 1 to 5, *characterised* in that it contains testosterone.

Penetration of a gestagen from a TTS through stratum corneum in a Franz cell



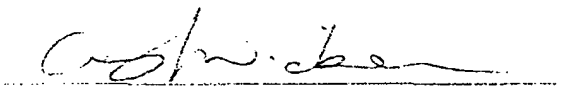
AUSTRALIA

DECLARATION

I, Dr A J Wickens, of 24 Honeypots Road, Mayford, Woking, surrey, GU22 9QW, England, do hereby declare that I am fully conversant with the English and German languages and that to the best of my knowledge and belief the following is a true translation made by me into the English language of International Patent Application PCT/EP/03229, Publication No. WO 97/03698, in the name of Labtech Gesellschaft für technologische Forschung und Entwicklung mbH.

Title: A hormone patch

Signed this 12 day of December 1997



A hormone patch

The present invention relates to a patch to be applied to the skin, which is also termed a transdermal therapeutic system (TTS), in which up to three drug substances are contained which are released from the TTS, through the skin, into the body (systemic circulation) of the human or of the animal. The dermal patch comprises a backing film and a pressure-sensitive adhesive in which the drug substances as well as other substances, for example resorption accelerators, are situated. In addition, a further adhesive layer is optionally provided, as is a protective film, which is removed by pulling it off before the patch is used.

Dermal patches for the transdermal administration of drug substances are known. One problem with these preparations is the resorption of sufficiently large amounts of active ingredient per unit area and per unit time, because many drug substances which are deposited on or stuck on to the skin in a topical preparation do not pass through the skin in sufficient amounts.

For this reason, so-called resorption accelerators, which are also termed penetration improvers, resorption promoters or enhancers, have been investigated and have been incorporated in dermal patches. In this manner, it has often been possible to achieve the desired pharmacological effect for the first time. Examples of resorption accelerators include propylene glycol, polyethylene glycols of lower molecular weight, oleic acid, isopropyl myristate, myristol, "Gattefossé" Transcutol, "Henkel" Eutanol, glycerol monolaurate (="Hüls" Imvitor 312), a partial glyceride of ricinoleic acid (="Hüls" Softigen 701), unsaturated polyglycolised glycerides (="Gattefossé" Labrafil M1944CS), "Gattefossé" Labrafac Hydro WL1219, Estasan GT60, saturated polyglycolised glycerides (="Gattefossé" Labrasol), phospholipids, etc. Further literature thereon: Rieg-Falson, F. *et al.* 1989, Watkinson, A.C. *et al.* 1991, and Hadgraft, J. and Guy, R.H. (eds.): Marcel Dekker Inc. N.Y. 1989.

This invention relates to the use of a mixture of the two substances oleic acid and 2-(2-ethoxyethoxy)ethanol jointly in a TTS as enhancers for oestrogens such as oestradiol and ethinyl oestradiol, gestagens such as norethisterone acetate, levonorgestrel or chlormadinone acetate and/or androgens such as testosterone.

In the context of our work on the development of dermal patches comprising different drug substances, a very large number of penetration improvers has been incorporated in the formulation, and the release of the active ingredient has been investigated. The latter has been tested in the USP paddle apparatus (described in United States Pharmacopoeia XXIII), penetration through "hairless mouse skin" has been tested using the Franz cell model (Franz cell: Franz, T.J., J. Invest. Dermatol. 1975 (64), pages 191-195), and penetration through human stratum corneum has likewise been tested in the Franz cell. The penetration-promoting substances comprised oleic acid DAB 10, 2-(2-ethoxyethoxy)ethanol, Eutanol G (DAB 10), Labrafac and Labrafil, as well as mixtures comprising oleic acid/2-(2-ethoxyethoxy)ethanol, oleic acid/Labrafil, and oleic acid/Labrafac, in a ratio of approximately 1:1.

The release of active ingredient with time in the USP paddle apparatus exhibited no great differences. On measuring the permeation through animal skin, and particularly through human stratum corneum, however, it was shown that dermal patches which were produced with a mixture of oleic acid and 2-(2-ethoxyethoxy)ethanol in a ratio of approximately 1:1 as enhancers gave significantly higher permeation rates than those which were observed on the addition of the individual enhancers or without enhancers. It was surprising that the mixture of oleic acid and 2-(2-ethoxyethoxy)ethanol gave permeation rates which were higher than those obtained when using mixtures of oleic acid and other enhancers. The former mixture is obviously distinguished by its special resorption-accelerating properties.

Moreover, it should also be emphasised as being advantageous that these are two known substances, which are customary and harmless as adjuvant substances in pharmaceutical preparations, and are not new chemical substances which would involve the risk of side-effects

and would have to be tested in long-term toxicological investigations before they could be employed in a medicine for human use.

Examples are given below of the manner in which dermal patches according to this Patent Application, and comparison patches, can be produced. Furthermore, the results on the release of active ingredient and the results of permeation tests are described. An HPLC method such as that which is familiar to one skilled in the art was employed for the analysis of the active ingredient content in the acceptor medium.

Claims

1. A transdermal therapeutic system (TTS) which contains
   - an oestrogen and a gestagen, or
   - a gestagen or
   - an androgen

   as drug substance(s), an acrylate-based pressure-sensitive adhesive, and the two substances oleic acid and 2-(2-ethoxyethoxy)ethanol as resorption promoters.

2. A drug preparation according to claim 1, characterised in that the oestrogen is oestradiol or ethinyl oestradiol and the gestagen is norethisterone acetate, levonorgestrel, progesterone or chlormadinone acetate, and the androgen is testosterone, wherein other salts or esters, or bases also, can also be used.

3. A drug preparation according to claims 1-2, characterised in that the acrylate-based pressure-sensitive adhesive is obtained by the radical polymerisation of butyl acrylate, 2-ethylhexyl acrylate, methacrylate, vinyl acetate, acrylic acid, hydroxyethyl acrylate or from mixtures of some or all of the cited monomers, and/or that crosslinking agents and/or other adjuvant substances are added in an amount less than 2 %.

4. A drug preparation according to claims 1-3, characterised in that the ratio by weight of oleic acid to 2-(2-ethoxyethoxy)ethanol is 2:1 to 1:2, preferably 1.5:1 to 1:1.5, and the amount of this mixture is 1 - 10 percent by weight with respect to the patch weight, including all the active ingredients and adjuvant substances, but without the films such as the backing film and the release liner.

5. A drug preparation according to claims 1-4, characterised in that it contains oestradiol and norethisterone acetate.

6. A drug preparation according to claims 1-4, characterised in that it contains oestradiol and levonorgestrel.

7. A drug preparation according to claims 1-4, characterised in that it contains ethinyl oestradiol and levonorgestrel.

8. A drug preparation according to claims 1-4, characterised in that it contains testosterone.

Penetration of a gestagen from a TTS through stratum corneum in a Franz cell